

A Randomized, Open-Label, Phase 3 Study Evaluating Efficacy and Safety of Gedatolisib With Endocrine Therapy (ET) and Palbociclib vs ET and Ribociclib as First-Line Treatment in Patients With HR-Positive and HER2-Negative Advanced Breast Cancer (VIKTORIA-2)

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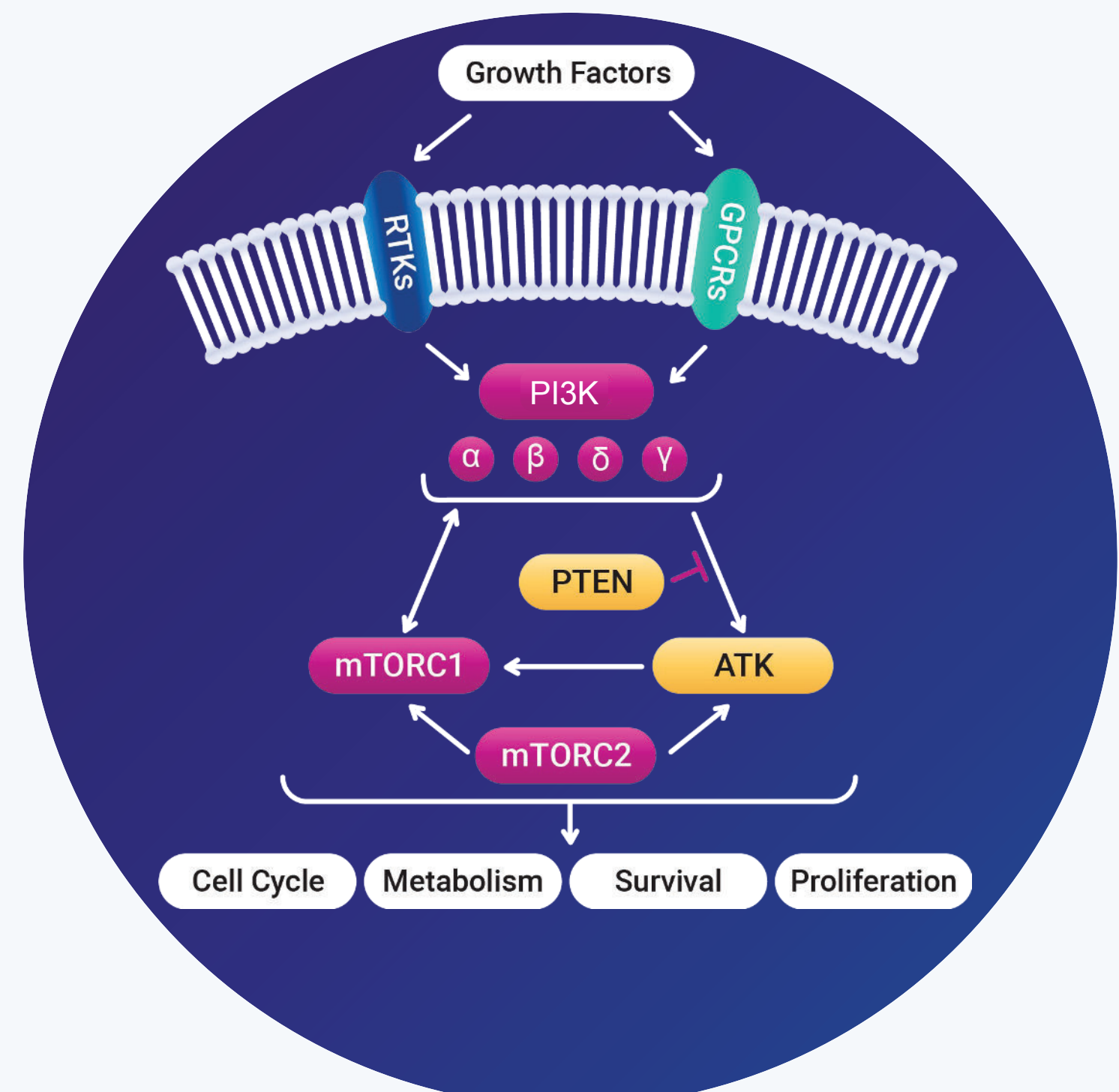
BACKGROUND

- For patients with hormone receptor–positive (HR+)/human epidermal growth factor receptor 2–negative (HER2–) advanced breast cancer (ABC), first-line treatment includes a cyclin-dependent kinase 4/6 (CDK4/6) inhibitor plus endocrine therapy (ET). Although endocrine-sensitive disease is associated with a median progression-free survival (PFS) of ~25–28 months, outcomes are poorer in patients with endocrine-resistant disease, defined as recurrence during or within 12 months of adjuvant ET.¹⁻⁴
- To improve outcomes in both endocrine-sensitive and endocrine-resistant first-line ABC, the addition of a phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT)/mechanistic target of rapamycin (mTOR) pathway (PAM pathway) inhibitor to palbociclib plus ET is being explored.
- Based on results from VIKTORIA-1 study 1, gedatolisib, a highly potent pan-PI3K/mTORC1/2 inhibitor is FDA approved in combination with fulvestrant, with or without palbociclib, for adults with HR+/HER2-, *PIK3CA*-WT locally advanced or metastatic breast cancer following progression on or after ≥1 line of endocrine therapy in the metastatic setting.^{5,6}
- Gedatolisib has also demonstrated clinical activity in the first-line setting; in a Phase 1b study of patients with treatment-naïve ABC, gedatolisib + palbociclib + letrozole achieved an overall response rate of 85.2%, median PFS of 48.4 months, and median overall survival (OS) of 77.3 months.^{7,8}
- Based on these findings, the Phase 3 VIKTORIA-2 trial was initiated to evaluate gedatolisib-based therapy in the first-line treatment of HR+/HER2– ABC.

MECHANISM OF ACTION

Gedatolisib is a first-in-class PAM inhibitor with a highly differentiated mechanism of action.⁹

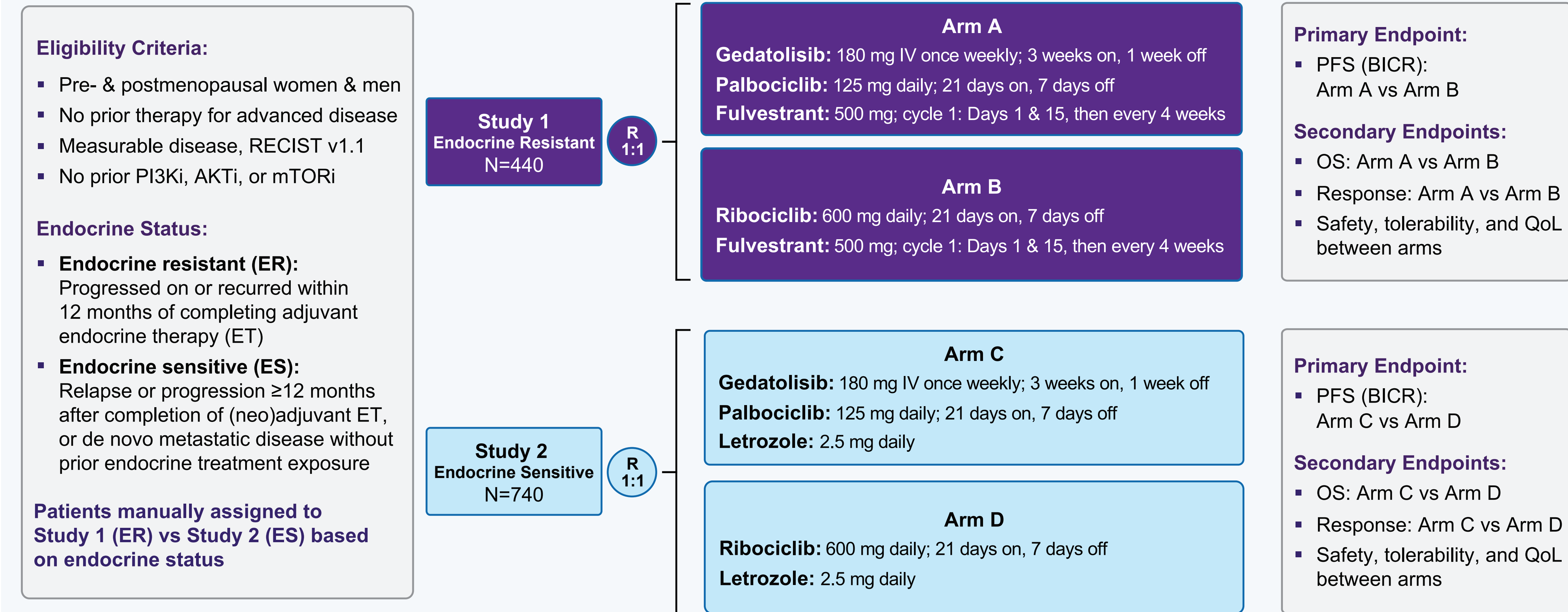
- Gedatolisib is an intravenously (IV) administered, multitarget PAM pathway inhibitor that targets all class I PI3K isoforms (α, β, δ, and γ) and the mTOR complexes mTORC1 and mTORC2 resulting in downstream inhibition of multiple effectors, including AKT.^{10,11}
- This multitarget blockage of the PAM pathway leads to antiproliferative effects in cancer cells regardless of *PIK3CA*, *PTEN*, or *AKT* mutational status.¹¹
- This mechanism may reduce the adaptive resistance that can emerge with single-target PAM pathway inhibitors.¹¹



AKT, protein kinase B; GPCR, G protein-coupled receptor; mTORC, mechanistic target of rapamycin complex; PI3K, phosphoinositide 3-kinase; PTEN, phosphatase and tensin homolog; RTK, receptor tyrosine kinase.

VIKTORIA-2 TRIAL DESIGN OVERVIEW

- VIKTORIA-2 (NCT06757634) is a multicenter, randomized, open-label Phase 3 trial evaluating the efficacy and safety of gedatolisib plus ET and palbociclib compared with ET and ribociclib as first-line therapy in patients with HR+/HER2– ABC. Participants are assigned to Study 1 (ET-resistant) or Study 2 (ET-sensitive) and randomized 1:1 to gedatolisib plus fulvestrant and palbociclib (Arm A) vs fulvestrant and ribociclib (Arm B) for Study 1 and gedatolisib plus letrozole and palbociclib (Arm C) vs letrozole and ribociclib (Arm D) for Study 2.



AKTi, protein kinase B inhibitor; BICR, blinded independent central review; ER, endocrine-resistant; ES, endocrine-sensitive; ET, endocrine therapy; IV, intravenous; mTORi, mechanistic target of rapamycin inhibitor; OS, overall survival; PFS, progression-free survival; PI3Ki, phosphoinositide 3-kinase inhibitor; QoL, quality of life; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors.

OBJECTIVES AND ENDPOINTS

STUDY 1

Primary Objective

- Compare the efficacy, as measured by PFS by blinded independent central review (BICR), of gedatolisib combined with palbociclib and fulvestrant (Arm A) vs ribociclib combined with fulvestrant (Arm B) in subjects with endocrine-resistant HR+/HER2– ABC who have not received any prior systemic anticancer therapy for advanced disease.

Key Secondary Objective

- Compare the efficacy, as measured by OS, between Arm A and Arm B in subjects with HR+/HER2– ABC who have not received any prior systemic anticancer therapy for advanced disease.

Additional Secondary Objectives

- Compare antitumor activity, change in health status/quality of life, and safety/tolerability between Arm A and Arm B.

STUDY 2

Primary Objective

- Compare the efficacy, as measured by PFS by BICR, of gedatolisib combined with palbociclib and letrozole (Arm C) vs ribociclib combined with letrozole (Arm D) in subjects with endocrine-sensitive HR+/HER2– ABC who have not received any prior systemic anticancer therapy for advanced disease.

Key Secondary Objective

- Compare the efficacy, as measured by OS, between Arm C and Arm D in subjects with HR+/HER2– ABC who have not received any prior systemic anticancer therapy for advanced disease.

Additional Secondary Objectives

- Compare antitumor activity, change in health status/quality of life, and safety/tolerability between Arm C and Arm D.

ELIGIBILITY CRITERIA

KEY INCLUSION CRITERIA

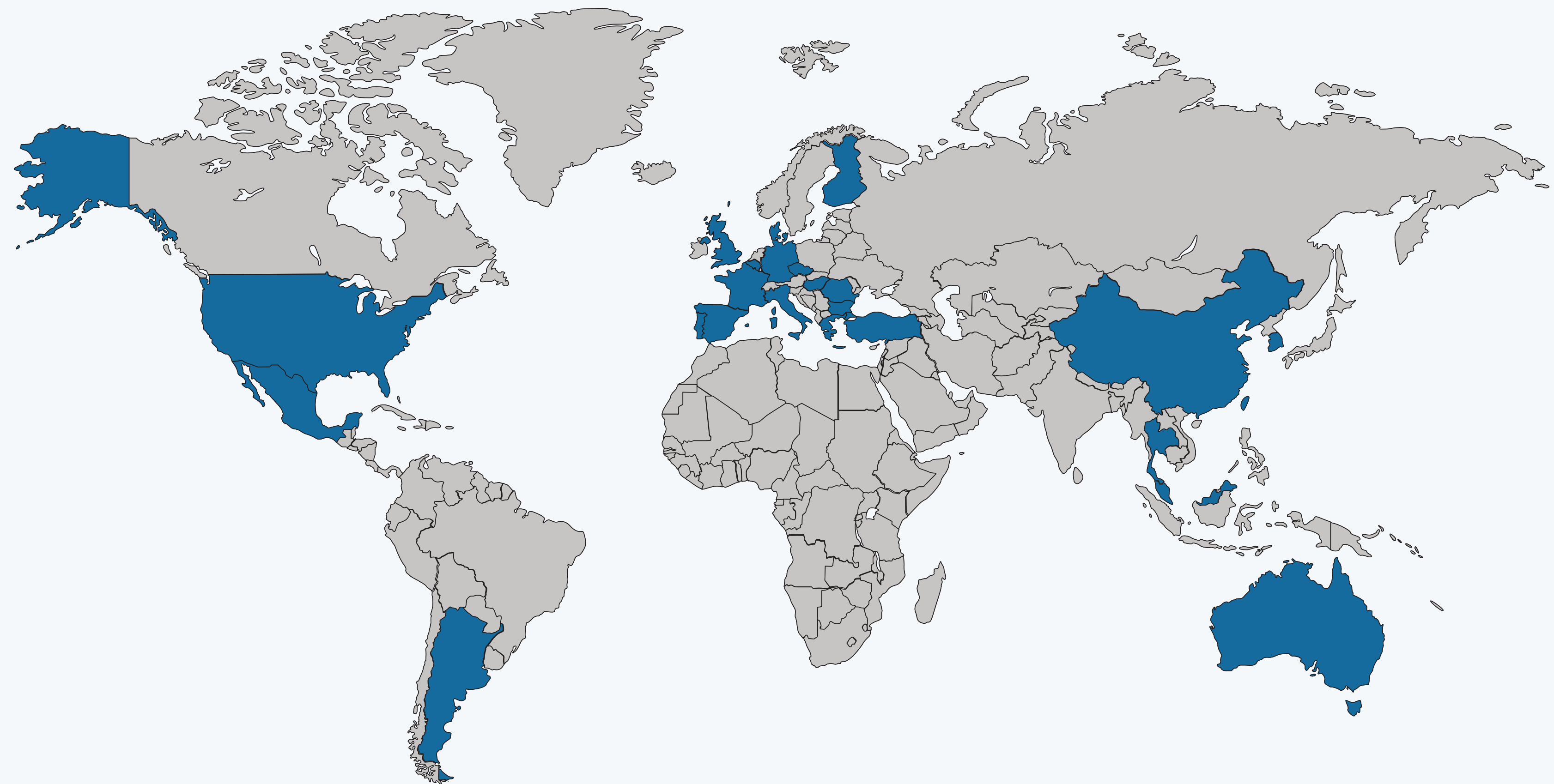
- Adults ≥18 years of age
- Confirmed diagnosis of HR+/HER2- breast cancer that is or has progressed to ABC- locally advanced and not amenable to resection and/or metastatic breast cancer
- Progression of disease during prior ET:
 - **Study 1:** Endocrine-resistant ABC defined as disease progression while receiving adjuvant ET or within 12 months of completing adjuvant ET
 - **Study 2:** Endocrine-sensitive ABC defined as disease relapse or progression ≥12 months after completion of at least 2 years of (neo)adjuvant ET or de novo metastatic disease without prior ET exposure
- Prior therapies permitted: (neo)adjuvant treatment with an aromatase inhibitor or tamoxifen; (neo)adjuvant fulvestrant only if the treatment duration was <6 months; (neo)adjuvant chemotherapy; (neo)adjuvant CDK4/6 inhibitor is allowed if the following criteria are met:
 - **Study 1:** If disease progression event occurred >6 months after completion of CDK4/6 inhibitor portion of treatment
 - **Study 2:** If disease progression occurred >12 months after completion of CDK4/6 inhibitor portion of treatment
- Confirmed diagnosis of estrogen receptor–positive and/or progesterone receptor–positive breast cancer as per American Society of Clinical Oncology/College of American Pathologists (ASCO-CAP) 2020 guidelines
- Documented HER2– as per ASCO-CAP 2018 guidance
- Radiologically confirmed measurable disease according to RECIST v1.1 per local assessment
- Consent for collection of a fresh tumor biopsy, an archival tumor tissue sample, or a liquid biopsy collection for central assessment of *PIK3CA* mutation status via specified test
- Eastern Cooperative Oncology Group performance status of 0–2
- Adequate bone marrow, hepatic, renal, and coagulation function as defined by acceptable laboratory parameters
- HbA1c ≤8%

KEY EXCLUSION CRITERIA

- Prior treatment with PI3K, AKT, or mTOR inhibitors
- Prior treatment with a selective estrogen receptor degrader, except fulvestrant, used in the (neo)adjuvant setting
- Prior treatment with systemic anticancer therapy for ABC
- Type 1 diabetes, or uncontrolled type 2 diabetes requiring daily insulin therapy for treatment of type 2 diabetes
- Untreated or active brain or leptomeningeal metastases
- Advanced, symptomatic, visceral spread that poses risk of near-term, life-threatening complications
- History of clinically significant cardiovascular abnormalities
- Pregnancy or breastfeeding

TRIAL STATUS

- VIKTORIA-2 is currently recruiting.
- Trial locations: United States, Argentina, Australia, Belgium, Bulgaria, China, Czechia, Denmark, Finland, France, Germany, Greece, Hungary, Italy, Malaysia, Mexico, Poland, Portugal, Romania, South Korea, Spain, Taiwan, Thailand, Turkey, United Kingdom.



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DISCLOSURES

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